Speculation Regarding Mechanisms Responsible for Acute Ischemic Heart Disease Syndromes*

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The factors responsible for the development of unstable angina pectoris, coronary artery spasm (Prinzmetal's angina) and acute myocardial ischemia or infarction, are not completely defined. Some patients with extensive and severe coronary artery stenoses do well with medical therapy, whereas others with similar or even less impressive coronary artery stenoses abruptly develop unstable ischemic heart disease. An improved insight into the mechanisms responsible for the conversion of chronic to acute coronary artery disease is essential to prevent acute myocardial infarction and sudden cardiac death. In this editorial, we have attempted 1) to examine the recent developments in our understanding of alterations in prostaglandin and serotonin production that may play a role in the development or perpetuation of acute ischemic heart disease, and 2) to speculate about the mechanisms responsible for coronary artery spasm.

Mechanisms Responsible for Myocardial Ischemia

Most patients with angina pectoris have significant fixed coronary artery stenoses. Two mechanisms are responsible for the development of myocardial ischemia: 1) increased myocardial oxygen demand, and 2) decreased myocardial perfusion and oxygen delivery. In most patients with stable angina, physical effort or emotion, with a resultant increase in heart rate, blood pressure or contractile state, or any combination thereof, increases myocardial oxygen demand without an adequate increase in oxygen delivery through tightly stenosed coronary arteries. As a result, myocardial ischemia develops. Occasionally, the patient with stable angina has a combination of effort and rest angina. In this circumstance, rest angina is probably caused by a decrease in myocardial oxygen delivery, perhaps resulting from coronary vasospasm or other mechanisms discussed later.

In contrast to typical stable angina, the acute ischemic heart disease syndromes (unstable angina, coronary artery spasm and acute myocardial infarction) are usually caused by a primary decrease in myocardial oxygen delivery (1–6). Both unstable angina and Prinzmetal's angina are caused by a primary reduction in myocardial oxygen delivery, but, in all probability, the mechanisms reponsible for the decrease in myocardial blood flow in these two syndromes are generally different. Acute myocardial infarction may complicate either unstable angina or coronary spasm when myocardial oxygen supply is diminished below critical levels for a sustained period (7).

Unstable Angina Pectoris

Unstable angina pectoris is defined as angina that increases in frequency, occurring with progressively less effort, and often at rest. Any factor that results in abrupt or progressive coronary artery luminal diameter narrowing may cause diminished myocardial perfusion at low levels of activity, or even at rest, with resultant ischemia and unstable angina. Table 1 lists several possible causes of unstable angina. In some patients, the syndrome may result from the progression of severe, multifocal coronary atherosclerosis. However, in many patients, other mechanisms are involved because there is not a good correlation between acute ischemic heart disease and the anatomic extent and severity of atherosclerosis.

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Table 1. Potential Causes of Unstable Angina Pectoris

1. Progressive coronary artery narrowing from atherosclerosis.
2. Platelet aggregation at the site of a coronary artery stenosis leading to increased luminal narrowing due to anatomic obstruction and dynamic changes in coronary vascular tone. See text for details.
3. Any combination of plaque fissure, hemorrhage or thrombosis with progressive coronary artery narrowing.
4. Coronary artery spasm.

Previous Evaluations of Alterations in Prostaglandin Metabolism in Patients With Unstable Angina

Clinical Studies

In 1979, we (8) tested the hypothesis that unstable angina is associated with transmyocardial alterations in thromboxane A_2 production. In 60 patients undergoing cardiac catheterization, blood samples were obtained from the coronary sinus and ascending aorta, and prostaglandins were measured by radioimmunoassay (8–10). By history, noninvasive evaluation and the results of cardiac catheterization, the patients were separated into five groups: Group A patients (n = 6) had congenital and acquired noncoronary cardiac lesions but were without significant coronary stenoses; Group B patients (n = 14) complained of chest pain but had no significant coronary artery stenoses or provokable coronary spasm; Group C patients (n = 18) had significant coronary artery disease and their most recent episode of chest pain occurred more than 96 hours before study; Group D patients (n = 15) had chest pain that had occurred 24 to 96 hours before study; and Group E patients (n = 7) had unstable angina with chest pain within 24 hours of study.

Thromboxane B_2 (the inactive metabolite of thromboxane A_2) concentrations were elevated across the coronary bed in Group E patients (those with continuing rest angina) (Fig. 1) and values in this group were significantly higher than those of patients in Groups A, B and C. Group D patients had a bimodal distribution; 12 patients had a low concentration and 3 had a markedly elevated value. It is not clear why three patients in Group D had elevated concentrations of thromboxane B_2. Two possible explanations include 1) persistent increases in cardiac thromboxane B_2 concentration after the relief of unstable angina pectoris, and 2) continuing unstable angina pectoris not detected clinically or identified by the patient.

Thus, these data demonstrate a temporal relation between continuing unstable angina pectoris and increases in transcardiac thromboxane B_2 concentration. These findings are consistent with the view that platelet aggregation is an important factor in the pathogenesis of unstable angina in patients.

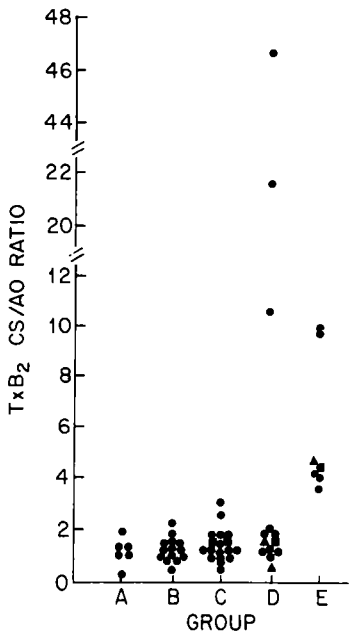

Figure 1. Ratios of thromboxane B_2 (TxB_2) in the coronary sinus (CS) and ascending aorta (AO) in the five groups of patients (n = 60) studied. Each **point** represents the data from one patient. **Squares** identify patients who received a cyclooxygenase inhibitor within 5 days of study, and **triangles** represent patients with coronary artery spasm. In Groups A (valvular and congenital nonischemic heart disease), B (chest pain syndrome without ischemic heart disease) and C (ischemic heart disease without chest pain for at least 96 hours), the patients had thromboxane B_2 coronary sinus/aorta ratios of 3.1 or less. Group D patients (unstable angina pectoris with chest pain 24 to 96 hours before study) had a bimodal distribution: 12 patients had low ratios, whereas 3 had very high ratios. Group E patients (unstable angina pectoris with chest pain within 24 hours before study) had ratios that were higher than those in patients in Groups A, B and C ($p < 0.05$). (Reprinted from Hirsh PD, et al. [8] with permission.)

Animal Studies

Thromboxane mechanisms. In the canine heart, a severe proximal coronary artery stenosis with associated endothelial injury causes cyclic coronary blood flow reductions (Fig. 2) (11,12). Dazoxiben (UK-37-248, a thromboxane synthetase inhibitor, Pfizer Pharmaceuticals) (12) or a thromboxane receptor antagonist (SQ 29,548, Squibb Pharmaceuticals) (13) abolished or significantly attenuated the frequency of cyclic flow reductions in approximately 80% of treated animals, whereas the frequency and magnitude of cyclic flow reductions were unchanged after the administration of saline solution. Thromboxane B_2 concentrations in the coronary artery and at the coronary stenosis were increased during cyclic flow reductions and reduced to control values after administration of dazoxiben (12). In contrast, 6-keto-prostaglandin F_{1a} (the inactive metabolite of prostacyclin) concentrations were reduced at the site of coro-

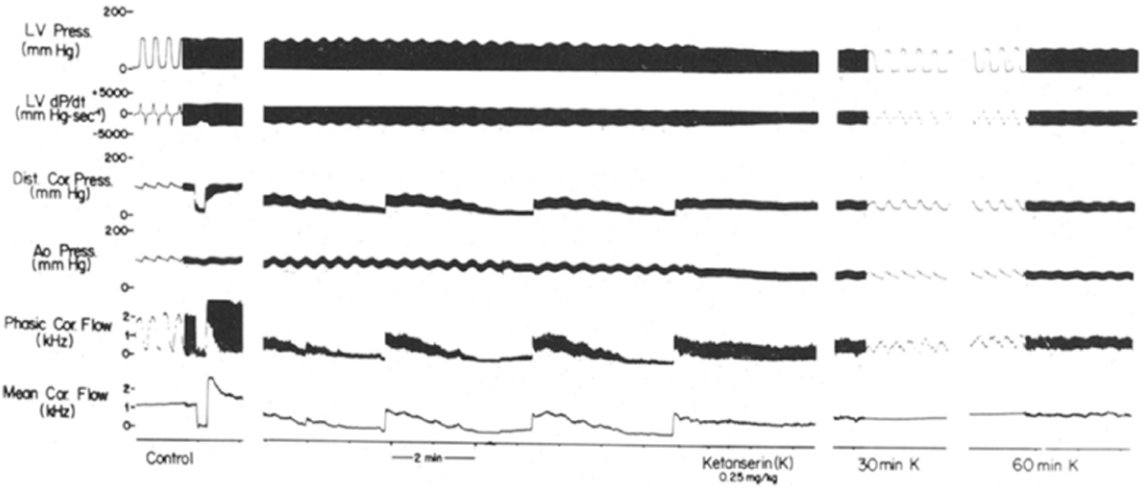

Figure 2. A representative recording from a dog with a severe coronary artery stenosis and cyclic flow alterations. Note the distal decline in coronary artery pressure and phasic and mean coronary blood flow during cyclic flow variations. Thromboxane synthesis inhibitors, thromboxane receptor antagonists and a serotonin receptor antagonist usually abolish or attenuate the cyclic flow variations. The effect of ketanserin (K) (a serotonin receptor antagonist) in abolishing the cyclic flow variations is demonstrated. Ao = aortic; Cor. = coronary; Dist. = distal; dP/dt = maximal rate of rise in pressure; LV = left ventricular; Press. = pressure. (Reprinted from Bush LR, et al. [15] with permission.)

nary artery constriction, and substantially less 6-keto-prostaglandin F_{1a} was synthesized after the in vitro addition of arachidonic acid as compared with that occurring in the nonconstricted, noninjured coronary artery (14). Distal coronary artery 6-keto-prostaglandin F_{1a} levels also increased significantly during cyclic flow reductions, and remained elevated after administration of dazoxiben (12). Systemically administered dazoxiben (2.5 mg/kg body weight, intravenously) suppressed arachidonic acid-induced thromboxane B_2 (but not prostaglandin E_2) production by canine platelets, but dazoxiben (1 μM) did not significantly affect prostacyclin synthesis by canine coronary artery rings (12).

Thus, thromboxane and prostacyclin concentrations increase substantially in the distal portion of a severely stenosed canine coronary artery. The thromboxane concentration also increases and the prostacyclin concentration decreases at the site of the stenosis in association with cyclic flow reductions. Furthermore, the administration of a thromboxane synthetase inhibitor (dazoxiben) or a thromboxane receptor antagonist (SQ 29,548) abolishes or markedly attenuates cyclic flow reductions, and the thromboxane synthetase inhibitor reduces the thromboxane concentration in the distal coronary artery beyond the site of coronary artery constriction.

Serotonin mechanisms. More recently, we have tested the hypotheses that aggregating platelets at the site of a tight proximal coronary artery stenosis release serotonin (5-hydroxytryptamine) and that serotonin is also an important factor in initiating or sustaining cyclic flow reductions in this same experimental model (15,16). Approximately 10 to 20% of animals fail to have their cyclic flow reductions abolished or markedly attenuated by a thromboxane synthetase inhibitor or receptor antagonist. Ketanserin, a serotonin receptor antagonist, usually abolishes cyclic flow reductions in this model and works in essentially every instance in which a thromboxane synthetase inhibitor or receptor antagonist, or both, has failed (Fig. 2) (15). In addition, the serotonin concentration increases 18- to 27-fold at the site of a coronary artery stenosis when cyclic flow reductions occur. Furthermore, after their abolition with ketanserin, cyclic flow reductions may be restored by the intraatrial administration of serotonin (16). Thus, both thromboxane and serotonin appear to be important in initiating or sustaining cyclic flow reductions, or both, in this experimental model. Moreover, if the contribution from either is eliminated or antagonized, cyclic flow reductions are usually terminated (17). Platelet aggregation can also be enhanced by the administration of platelet activating factor (18) (a product released in various inflammatory reactions), adenosine diphosphate and the activation of alpha-2-adrenergic receptors (19). However, in the canine model, alpha-adrenergic antagonists have a relatively weak effect on platelet aggregation (15).

Influence of Aspirin in Patients With Unstable Angina

If platelet aggregation and the consequent release of thromboxane and serotonin are important in the initiation or sustaining of unstable angina, an intervention that interferes with platelet aggregation and the subsequent release

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of these humoral mediators should reduce morbidity and mortality in patients with this clinical syndrome. Indeed, recent clinical studies (20,21) have shown that aspirin, an inhibitor of cyclooyxygenase, thromboxane synthesis and platelet aggregation, reduces the risk of subsequent myocardial infarction and death in patients with unstable angina. Specifically, a multicenter Veterans Administration hospital study (20) established that 1 tablet of aspirin (300 mg/day) reduces mortality and the risk of myocardial infarction in the weeks after the onset of unstable angina in men. More recently, a Canadian study (21) demonstrated that the equivalent of 4 aspirin tablets/day reduces mortality and the risk of subsequent myocardial infarction in the ensuing 2 years in men and women with unstable angina. These data are consistent with the hypothesis that platelet aggregation and subsequent increases in local thromboxane and serotonin concentrations may play a role in causing acute myocardial infarction or death, or both, in patients with unstable angina. They also suggest that the inhibition of the thromboxane effect is of clinical benefit in patients with unstable angina, even if the prostacyclin concentration is also reduced (as occurs with the higher doses of aspirin).

Platelet aggregation and coronary thrombosis. We have speculated previously that sudden death and acute myocardial infarction (7) may result from progressive platelet aggregation with concomitant local increases in thromboxane and serotonin concentrations. Such increases within a stenosed coronary artery contribute to platelet aggregation and dynamic increases in coronary vascular tone (Fig. 3). When coronary arteries are occluded or narrowed for a sufficient period of time by these mechanisms, myocardial necrosis or electrical instability and sudden death may occur (7). Ambrose et al. (22) showed that the morphologic appearance of narrowed coronary arteries in patients with unstable angina and acute transmural myocardial infarction is similar, and is characterized by an eccentric stenosis with a narrow neck presumably reflecting a partially occluding coronary thrombus at a severe coronary artery stenosis. Thus, unstable angina and acute myocardial infarction probably represent a continuum in relation to the process of coronary artery thrombosis (7,22). Increased local concentrations of histamine, platelet activating factor or leukotrienes released from aggregating platelets or infiltrating white cells may also increase coronary vascular tone, promote platelet aggregation and contribute to the development of unstable angina or acute myocardial infarction.

Coronary Artery Spasm

We believe that Prinzmetal's angina, the syndrome of chest pain occurring at rest associated with focal obliteration (spasm) of the lumen of a large epicardial coronary artery and transient ST segment deviation (usually elevation) and

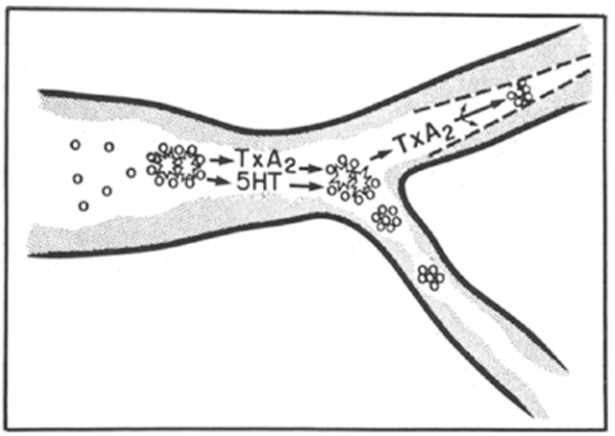

Figure 3. A schematic diagram indicating the possible mechanisms by which thromboxane A_2 (TxA_2) and serotonin (5HT) promote platelet aggregation and decrease coronary blood flow in the patient with angina. Aggregating platelets (**stars**) release thromboxane A_2 and serotonin, which cause further platelet aggregation downstream and dynamic alterations in coronary vascular tone. See text for details. (Modified with permission from Hirsch PD, Campbell WB, Willerson JT, Hillis LD. Prostaglandins and ischemic heart disease. Am J Med 1981;71:1009–26.)

unstable angina generally have different pathophysiologic mechanisms. Coronary artery spasm, as it manifests itself in Prinzmetal's angina, ordinarily responds well to one of the slow channel calcium blockers with or without nitrates (23). Patients with Prinzmetal's angina occasionally present with unstable angina or acute myocardial infarction, but, in a large number of patients, it has not been possible to demonstrate by coronary arteriography and clinical observations that coronary spasm is the pathophysiologic event generally leading to unstable angina or acute myocardial infarction.

Mechanisms. The mechanisms responsible for coronary artery spasm have not been elucidated. Most patients with spasm are heavy smokers and smoking itself may cause coronary vasoconstriction mediated, at least in part, through alpha-adrenergic mechanisms (24). Studies from our institution (25) have failed to demonstrate genetic transmission of coronary artery spasm. Apart from slow channel calcium blockers and nitrates, no therapeutic intervention has proved uniformly effective in treating patients with Prinzmetal's angina (26–30). Histamine and ergonovine have provoked coronary artery spasm in atherosclerotic swine and canine models (31,32), and vasopressin has been shown occasionally to provoke coronary spasm in patients (Pitt B, personal communication, 1986). Morphologic evaluations of coronary arteries that have demonstrated spasm during life are few in number, but one recent evaluation (33) suggested an increased number of mast cells in the adventitia, thereby leading to speculation that humoral mediators released from infiltrating mast cells, such as histamine, serotonin or prostaglandin D2, may be responsible for the development of coronary artery spasm.

Etiology. Because the provocative influences and effectiveness of selected therapeutic regimens vary among patients with coronary artery spasm, the etiology of spasm may also vary from one subject to another. Approximately three-fourths of patients with coronary vasospasm have significant atherosclerotic stenoses. Etiologic possibilities to explain vasospasm include altered autonomic neural control, altered contractile function and local release of vasoactive mediators. There is little direct support for the first two possibilities. We postulate that the exaggerated local contractile response of coronary artery spasm results from the release of humoral mediators due to 1) focal intimal endothelial damage and the consequent accumulation of platelets and white cells at the site of endothelial injury, or 2) infiltration of white cells and mast cells in the adventitia and interior portions of the artery as a consequence of injury or progression of vascular disease, or both. The mechanisms responsible for endothelial or vascular injury probably vary among patients, but may be immunologically mediated, the result of mechanical injury or related to atherosclerosis or infection.

We postulate that vascular injury may lead to an exaggerated coronary vascular contractile response (coronary artery spasm) when the appropriate concentrations of vasoconstrictors, including single or combined increases in serotonin, thromboxane, prostaglandin D_2, histamine, platelet activating factor, selected leukotrienes and vasopressin, occur locally. This is especially likely when intrinsic vasodilator substances (prostacyclin or endothelial-derived relaxing factor) or intrinsic substances that act to prevent thrombus development (prostacyclin or tissue plasminogen activating factor) are diminished or absent because of endothelial injury or when their effect is antagonized by an inhibitor at the same site (34–36). In these individuals, the slow channel calcium blockers and nitrates, alone or in combination, are effective, because they reduce coronary vascular contractile responses to different stimuli independent of specific mechanisms causing coronary artery spasm.

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